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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/226,794	01/07/1999	WALDEMAR DEBINSKI	6460-4	9546

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	24

DATE MAILED: 05/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/226,794	Debrinski et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 1, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-6, and 14-22* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-6, and 14-22* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

1. The Declaration filed March 1, 2002 (Paper No. 22) and the Amendment filed March 1, 2002 (Paper No. 23) in response to the Office Action of November 6, 2001 (Paper No. 20) are acknowledged and have been entered. Previously pending claims 1 and 18 have been amended. Claims 1, 2, 4-6, 14-22 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 103

4. Claims 1, 2, 4-6 and 14-22 remain rejected under 35 USC 103 for the reasons previously set forth in Paper No. 20, Section 4, pages 2-7 and in Section 5, pages 7-11.

Applicant argues that without relying on the Debinski abstract there is no *prima facie* case of obviousness since the Debinski Paper discloses that established glioma cell lines and primary cultures of glioblastoma multiform cells are sensitive to hIL13-based toxins in *in vitro* assays and none of the experiments of the Debinski Paper were performed *in situ* and as previously indicated there are significant differences between *in vitro* assays and the *in situ/in vivo* situation and the Debinski Paper doesn't teach anything about IL13 receptor expression *in vivo*. Further, the "explant cells" the Office Actions refers to are not simply cells that were removed from a patient and immediately tested for IL13 receptor expression but rather the cells were processed and then cultured, thus the phrase "explant cells" refers to an *in vitro* cell culture and not a freshly excised tissue sample.

The argument has been considered but has not been found persuasive because although the Debinski abstract confirms the findings of the Debinski paper, even without that confirmation, it would have been obvious, and one of ordinary skill in the art would have expected to and have been motivated to treat glioma cells, *in vivo* with the known product, given what was known in the art and the clear teaching that the primary explant cells overexpressed the receptor. As previously disclosed, the primary explant cells in Debinski et al are not an established cell line and were enriched for hIL13 binding sites compared to the established cell lines. Further, because the primary cells are not an established cell line, they would not be expected to have developed the artifacts sometimes seen in established cell lines. Although the specification teaches and Applicant argued previously that recent studies on GBM showed than an antigen of high specificity that is present is completely lost in cell culture or that the cultured cells overexpressed a molecule which was not overexpressed *in situ*, these teachings are drawn to established cell lines. In particular, a review of Zellner et al (Clin. Can. Res, 1998, 4:1797-1802), relied upon by the specification to teach that glioma cells in culture overexpress products not overexpressed *in vivo*, revealed that the glioma derived cell lines used there were not primary explants in culture, but rather were an established cell line that had been in culture for at least three years at the time the reference was published (p. 1798). Further, as previously stated, the Debinski paper specifically stated that these hIL13 receptors represent a new attractive target for the treatment of brain cancers. The claimed invention is obvious over the combined references, without the added corroboration of the Debinski abstract for the reasons previously

set forth, especially in light of the specific statement in the Debinski paper that, given the findings in the primary explant cells, that the hIL13 receptors are a target for the treatment of brain cancers. Since Inventor Debinski is clearly one of skill in the art and first author on the referenced paper, it is clear that one of skill in the art would have been motivated to treat for the reasons of record and would have believed that it is more likely than not that the hIL13 receptor is an appropriate target for the treatment of gliomal brain cancers. Applicant's arguments have not been found persuasive and the rejection is maintained.

Further, as drawn to the newly added limitation of contacting a glioma cell contained within the cranium of the mammalian subject in claims 18 and the claims dependent on claim 18, the claims remain rejected for the reasons of record and further are rejected further in view of Sashira (Med. J. Kagoshima Univ, 1986, 38:15-48) who, although drawn to chemotherapy cancer treatment and not immunotoxins cancer is clearly relevant to the instant rejection. Sashira teaches that intratumoral administration of drugs for the treatment of brain tumor by-passes the blood-brain barrier and exposes the neoplastic tissue directly to the drugs and allows high concentration of drugs into the tumor with very low passage of the compounds into the blood stream, therefore considerably reducing systemic toxicity. The reference concludes that intratumoral therapy is useful not only for induction therapy but also as maintenance therapy (see abstract). Thus, it would have been *prima facie* obvious to one of ordinary skill in the art and one of ordinary skill in the art would have been motivated, at the time the invention was made, to

contact the glioma cell contained within the cranium by intratumoral injection because Sashira specifically teaches the usefulness of the method of administration.

Applicant argues that the BioCentury Article does not teach or suggest intratumor injection. The argument has been considered but has not been found persuasive in view of the Sashira reference above.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claims 1, 2, 4-6 and 14-22 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a receptor that binds IL13 with a greater affinity than it binds IL4 recited in claims 1 and 18 has no clear support in the specification and the claims as originally filed. a review of the specification did not reveal support for the newly added limitation. Applicant argues in Paper No. 23 that the Examiner's indication that this phraseology is clear means that this language would satisfy the written description requirement of section 112. The argument has been considered but has not been found persuasive because the specification does not support the language, further, it is equally possible that the preferential binding is a result of increased avidity rather than affinity. The subject matter claimed in claims 1, 2, 4,-6 and 14-22 broadens the scope of the invention as originally disclosed in the specification.

7. Claim 18 and the claims dependent upon claim 18 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "contacting the glioma cell contained within the cranium of the mammalian subject" recited in claim 18 has no clear

support in the specification and the claims as originally filed. A review of the specification revealed support for intratumor injection into a subcutaneous mouse tumor (p.4, line 10), inhibiting the growth of a tumor by delivering into the subject a molecule (p. 3, lines 1-7) but not support for contacting the glioma cell contained within the cranium of the mammalian subject. The subject matter claimed in claims 18 and the claims dependent upon claim 18 broadens the scope of the invention as originally disclosed in the specification.

8. All other objections and rejections in Paper No. 20 are withdrawn.

9. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

a SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT a FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

(703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1640.

Susan Ungar,
Primary Patent Examiner
April 26, 2002